

Air Toxics in Relation to Autism Diagnosis, Phenotype, and Severity in a U.S. Family-Based Study

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BACKGROUND: Previous studies have reported associations of perinatal exposure to air toxics, including some metals and volatile organic compounds, with autism spectrum disorder (ASD).

OBJECTIVES: Our goal was to further explore associations of perinatal air toxics with ASD and associated quantitative traits in high-risk multiplex families.

METHODS: We included participants of a U.S. family-based study [the Autism Genetic Resource Exchange (AGRE)] who were born between 1994 and 2007 and had address information. We assessed associations between average annual concentrations at birth for each of 155 air toxics from the U.S. EPA emissions-based National-scale Air Toxics Assessment and *a*) ASD diagnosis (1,540 cases and 477 controls); *b*) a continuous measure of autism-related traits, the Social Responsiveness Scale (SRS, among 1,272 cases and controls); and *c*) a measure of autism severity, the Calibrated Severity Score (among 1,380 cases). In addition to the individual's air toxic level, mixed models (clustering on family) included the family mean air toxic level, birth year, and census covariates, with consideration of the false discovery rate.

RESULTS: ASD diagnosis was positively associated with propionaldehyde, methyl *tert*-butyl ether (MTBE), bromoform, 1,4-dioxane, dibenzofurans, and glycol ethers and was inversely associated with 1,4-dichlorobenzene, 4,4'-methylene diphenyl diisocyanate (MDI), benzidine, and ethyl carbamate (urethane). These associations were robust to adjustment in two-pollutant models. Autism severity was associated positively with carbon disulfide and chlorobenzene, and negatively with 1,4-dichlorobenzene. There were no associations with the SRS.

CONCLUSIONS: Some air toxics were associated with ASD risk and severity, including some traffic-related air pollutants and newly-reported associations, but other previously reported associations with metals and volatile organic compounds were not reproducible. <https://doi.org/10.1289/EHP1867>

Autism spectrum disorder (ASD) is a serious developmental disability with a U.S. prevalence of 1 in 68 among 8-y-olds (Christensen et al. 2016). ASD etiology is multifactorial, caused in part by genetics, with inheritance estimates of 50% (Sandin et al. 2014). Other suggested causes include environmental chemical exposures during the period of rapid brain development in pregnancy and early postnatal life (Kalkbrenner et al. 2014; Lyall et al. 2016). Understanding the contribution of environmental factors to ASD is important, as these factors may be amenable to intervention, and may operate on specific inherited backgrounds.

Humans are exposed to hundreds of environmental chemicals by inhaling ambient air. Air pollution is a complex mixture of often spatially correlated metals, volatile organic compounds, and particles. The air pollutant, fine particulate matter ≤ 2.5 μm in aerodynamic diameter (PM_{2.5}), has been shown to be associated with ASD in several studies and a meta-analysis (Becerra et al. 2013; Volk et al. 2013, Lam et al. 2016). Although PM_{2.5} and five other criteria pollutants are monitored extensively in the United States,

hundreds of other air pollutants have historically been monitored less frequently, that is, the metals and volatile organic compounds termed air toxics (also known as hazardous air pollutants). Air toxics arise from vehicle emissions (traffic pollution), factory and power plant smokestacks, and small widely distributed sources like gas stations and dry cleaners. Sources of air toxics overlap with those of PM_{2.5}, with an especially important source being traffic-related air pollution—considered a primary source of PM_{2.5}. However, air toxics are often studied separately from criteria air pollutants because methods for their assessment and quantification vary. Air toxics are important to study with regard to ASD because they have established toxicity, have some evidence of association with autism in a small number of prior studies, and constitute potentially modifiable risk factors (U.S. EPA 2017).

Prior studies of air toxics and ASD were population-based and nested case-control studies conducted in different regions of the United States (see Table S1) (Kalkbrenner et al. 2010; Roberts et al. 2013; Talbott et al. 2015; von Ehrenstein et al. 2014; Windham et al. 2006). These studies included between 11 and 35 air toxics in primary analyses. Various solvents and metals were found to be associated with ASD, although results for individual air toxics varied by study. Air toxics positively associated in at least one of these studies included 1,2,4-trichlorobenzene, 1,3-butadiene, acetaldehyde, benzene, cadmium, chromium, copper, diesel particulate matter, ethyl benzene, formaldehyde, lead, manganese, mercury, methylene chloride, nickel, quinoline, styrene, tetrachloroethylene (perchloroethylene), toluene, trichloroethylene, vinyl chloride, and xylenes (see Table S1). Whether each of these air toxics plays a role in contributing to ASD is still in question due to limited replication of results for individual air toxics. Additionally, questions remain about whether an association with a given air toxic may be driven by a different, correlated

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pollutant, and resolving this potential confounding is important for determining an appropriate regulatory response.

To extend the understanding of the roles of air toxics in ASD etiology, we conducted a study using a different design than previously, with unique strengths. In a multiplex family-based study of individuals residing across the United States, it was possible to account for some unmeasured family-level confounders and to examine associations in the context of high genetic risk. In addition to examining risk for ASD diagnosis, we examined autism-related neurodevelopmental impairment, including autistic traits and autism severity. We examined a larger number of air toxics than previously studied—considering an initial list of 182 air toxics—to evaluate consistency with prior findings and to examine effects of additional air toxics that have been little studied. Finally, we were able to partially address the role of air pollutant mixtures by conducting some pairwise adjustments of one air toxic for another.

Methods

Study Sample

Our study sample comprised individuals from the Autism Genetic Resource Exchange (AGRE), a volunteer research repository of families from across the United States in which typically two or more siblings have a diagnosis of ASD (multiplex families). AGRE was formed in 1997 to create a large data repository of autism phenotype information and biomaterials to facilitate genetic studies of autism (<https://research.agre.org/?CFID=572128&CFTOKEN=8010>), with IRB oversight from the University of Pennsylvania School of Medicine (Geschwind et al. 2001), and includes over 1,700 families (Autism Genetic Resource Exchange 2016). AGRE recruitment methods and phenotype characterization have been described in detail elsewhere (Goin-Kochel et al. 2008). Briefly, participating families self-referred into AGRE. Once interest was indicated, enrollment materials and informed consent were collected by AGRE staff and participation in the assessment battery and biosample collection began. Each AGRE family has the option to discontinue participation at any time and to indicate a willingness to be contacted for additional research studies. For this study, we included families with at least one birth between 1994 and 2007 to correspond to the period when high quality data on the air pollutant exposures studied here were available, and to allow at least 5 y of follow-up until our study start in 2012 for a possible diagnosis of ASD. This resulted in 3,342 participants from 1,466 families as our starting AGRE population.

Autism Assessment

We analyzed three outcome measures pertaining to autism diagnosis and phenotype: *a*) an ASD diagnosis; *b*) a continuous measure of the broader autism phenotype among cases and controls, using the Social Responsiveness Scale (SRS); and *c*) a measure of the severity of the autism symptoms only among those meeting diagnostic criteria for ASD, using the Calibrated Severity Score (CSS).

ASD diagnosis for all AGRE participants was based on a well-validated parent interview autism research tool, the Autism Diagnostic Interview–Revised (ADI-R) (Le Couteur et al. 1989). After scoring, participants were categorized as Autism, Not Quite Autism (NQA), Broad Spectrum, and Not Met. For research purposes, AGRE defines the NQA category as “no more than one point away from meeting autism criteria on any or all of the three ‘content’ domains (i.e., social, communication, and/or repetitive behavior) and meeting criteria on the ‘age of onset’ domain; or, individuals who meet criteria on all three ‘content’ domains, but do not meet criteria on the ‘age of onset’ domain.” The Broad

Spectrum category is defined by AGRE as “patterns of impairment along the spectrum of pervasive developmental disorders” (AGRE 2016). For this study, we defined ASD diagnosis as a participant classified as Autism, NQA, or Broad Spectrum, consistent with AGRE standard practice (Lajonchere and AGRE Consortium 2010). Participants categorized by AGRE as Not Met or with missing status were considered not to have an ASD diagnosis.

All AGRE participants (including unaffected siblings) were invited to complete the SRS, as part of other AGRE collaborations (Constantino et al. 2003), but only about 63% did so. Although the SRS was developed as a clinical screening tool to distinguish autism from other childhood psychiatric conditions, it has been used in research as a valid quantitative measure of autistic traits in children 4–18 y of age. The SRS has 65 items with Likert-scale responses normed to a mean of 50 points, with higher scores indicating more autistic traits. For this analysis, we included the total *t*-score of the SRS when completed by a parent of the index participant within the recommended age range (4–18 y).

Lastly, to address the degree of autism severity among AGRE participants designated as having ASD, we included a score constructed from items of a research tool for autism based on direct observation, the Autism Diagnostic Observation Schedule (ADOS) (Lord et al. 1989). ADOS raw scores were mapped to CSSs based on the algorithm developed by Gotham et al. (2009). The CSS is a standardized metric for comparing autism severity across chronological ages and IQ points. The CSS ranges from 1 to 10, with higher scores indicating more severe autism.

Address Collection and Geocoding Process

We linked concentrations of multiple air toxic pollutants to AGRE participants using individual-level geographic and temporal information. We focused on the home address of the family during the pregnancy with each index participant because of evidence that pregnancy and early life is a period when exogenous exposures may contribute to ASD.

We collaborated with AGRE to obtain participant addresses in two ways. First, all AGRE families with at least one member born between 1994 and 2007 were approached to complete an online residential history questionnaire recording residence dates and addresses. To supplement these data, we performed a LexisNexis search to gather address history data when the study contact listed for an AGRE family was the biological mother. LexisNexis is an aggregator of consumer (e.g., credit) and public (e.g., voter registration, department of motor vehicles) records that provides address history search services. The accuracy of LexisNexis residential tracing has compared favorably to self-report (Jacquez et al. 2011). After integration of the two sources to obtain the largest possible sample size, we removed participants who did not have an address falling in the period from 1 y before through 2 y after the date of birth of the participant. If more than one address was returned by LexisNexis and the address dates were sequential and consistent, gaps between addresses were filled by splitting time between subsequent addresses. For example, if the end date of an address was listed as 1 July 2000 and the start of the next sequential address was 1 August 2000, then 15 July 2000 (the mid-point between the two) was considered to be the move date. We used the date of birth to assign the air toxics exposure, prioritizing the self-reported address history over the LexisNexis address history when both were available. When LexisNexis address histories contained multiple addresses corresponding to the birth date, we used the address with the highest proprietary confidence ranking algorithm. We excluded 5 participants who at birth resided outside of the contiguous United States, resulting in 2,489 participants with an air toxics exposure assignment (74% of the 3,342 eligible based on birth year).

We determined the spatial coordinates for the birth address using ArcGIS and the Texas A&M Geocoder. We then used spatial joins within the Texas A&M Geocoder to determine the census tract and census block group corresponding to the birth address for each included AGRE participant. We assigned both 1990 and 2000 census boundaries, which have slight differences, because both were needed for linking to air toxics and census variables.

Air Toxics Assessment

Air toxics concentrations were obtained from the emissions-based model of the U.S. EPA, the National-scale Air Toxics Assessment (NATA) (U.S. EPA 2016; Rosenbaum et al. 1999). NATA models were created and run every 3 y during this study period to create census-tract estimates for the year. We linked the NATA model closest in time to the birth year as follows: NATA 1996 for birth years 1994–1997, NATA 1999 for birth years 1998–2000, NATA 2002 for birth years 2001–2003, and NATA 2005 for birth years 2004–2007. The NATA model uses inputs from the National Emissions Inventory, which includes emissions from smokestacks as reported to the Toxics Releases Inventory; traffic volume and location; other national, regional, and local emissions information; chemical transformation in the atmosphere; and weather information, to generate the average ambient concentration of multiple air toxics for each U.S. census tract. NATA uses the Assessment System for Population Exposure Nationwide (ASPEN) framework to simulate the behavior of the air toxics once emitted into the atmosphere, for example, by assuming certain distribution patterns and secondary pollutant formation (Rosenbaum et al. 1999). The model has been validated showing good agreement between modeled and measured values, but with differences by region (Payne-Sturges et al. 2003; Pratt et al. 2000; Rosenbaum et al. 1999; State of New Jersey 2001). The number of air toxics modeled by the U.S. EPA was much smaller in 1996 (33 air toxics) and then was expanded for model years 1999, 2002, 2005 (although the exact list of available air toxics differed slightly across years.) For a few air toxics, we consulted NATA technical documentation to combine air toxics with slight differences across years: chromium III/VI, polycyclic organic matter (POM), and polycyclic aromatic hydrocarbons (PAH). When a given air toxic was not available for a certain year, we treated that observation as missing rather than filling in with an earlier or later year. Therefore, the sample size available for analysis varied across air toxics.

Covariates

Characteristics of AGRE participants, such as year of birth, race/ethnicity, number of siblings in the family, and maternal age, were obtained from AGRE datasets. To enrich the information on the neighborhood environment, which may be related to air toxic concentrations, we linked to census data using the block group pertaining to the index participant's birth address. Census block group variables pertaining to population density, percentage with a high school education or more, and median rent were spatially smoothed and scaled to percentile values.

Statistical Methods

We included 155 air toxics with a sufficient proportion detected, defined as at least 10% with non-zero concentrations (resulting in 25 excluded air toxics), and with sufficient variability in this dataset, defined as air toxics for which the 95% concentration was at least twice the 5% concentration (resulting in two additional excluded air toxics) (see Table S2). Results were scaled to the difference between the 75th and 25th percentile for each pollutant except for six air toxics with a 75th percentile value of 0, for which we contrasted the 95th percentile value to 0. We truncated

air toxics concentrations with highly skewed distributions by replacing those values that were outside $Q1 - (3 \times IQR)$ and $Q3 + (3 \times IQR)$ at $Q1 - (3 \times IQR)$ and $Q3 + (3 \times IQR)$. We compared the model fits of truncated air toxics with those of log-transformed air toxics in models predicting ASD diagnosis, concluding that log-transformed air toxics produced a better fit on average, based on a lower Akaike information criterion value (Akaike 1974). In log transformation, zeros were replaced by the half of the minimum positive non-zero value in our sample.

To present and compare results taking into consideration common sources or spatial patterns of air toxics, we placed air toxics into correlation groups with at least moderate pair-wise correlations ($r > 0.7$). These groups were used to order results in tables, not to create indices or factor scores as predictors in statistical models. To create the groups, we used hierarchical clustering, with an agglomerative method using complete distance (Defays 1977), where distance was defined as $\sqrt{1 - r^2}$ and r was the correlation of the log-transformed air toxics, specifying groups with a minimum correlation greater than the absolute value of 0.7. The method was robust to the impact of missing observations across a large number of air toxics; the missing pattern precluded using principal components analysis.

Our primary models produced effect estimates for each air toxic singly as a predictor of three separate autism-related endpoints: *a*) odds ratios (ORs) and 95% confidence intervals (CIs) from logistic regression comparing participants with an ASD diagnosis to siblings who were not diagnosed with ASD (1,540 cases and 477 controls), *b*) change in SRS total *t*-score using linear regression ($n = 1,272$ cases and controls combined), and *c*) change in CSS using linear regression among participants with an ASD diagnosis ($n = 1,380$). To account for similarities among siblings, all models were mixed models with a random effect for the family. To adjust for unmeasured family-level factors that are predictive of air toxic exposures and may confound associations, we modeled an individual participant's air toxic concentration adjusted for the average of the same air toxic concentration calculated for that participant's family group, following the method of Begg and Parides (2003). This modeling approach leverages the information available in a dataset of siblings nested within families. It assumes that focusing on how a given participant's air toxic exposure differs from his/her siblings is more likely to be an unbiased measure of exposure and accounts for the average air toxic level in the family, which may be influenced by social class confounding, inherited genomic susceptibility, or other family-level factors. All models were adjusted for the participant's birth year to account for temporal trends (including maternal age across sibling births, trends in ASD diagnosis rates over time, and differences across NATA model years) and adjusted for census block group variables. To account for the large number of statistical comparisons, we used the Benjamini-Hochberg approach with the false discovery rate (FDR) set at the 0.1 level, to limit the proportion of our significant findings that will be false positive to 10% (Benjamini and Hochberg 1995).

We performed a sensitivity analysis to evaluate the impact of air toxics exposure measurement error due to time lags between the year of the NATA estimate and the year of the child's birth, by restricting to birth years when the pregnancy likely overlapped the years of the NATA estimates (e.g., 1996, 1997, 1999, 2000, 2002, 2003, 2005, 2006). We hypothesized that these ORs would be greater in magnitude due to reduced exposure measurement error. This sample was approximately 60% of the original sample: 940 with autism and 283 without, from 772 families.

We evaluated the extent to which our main findings may have been influenced by confounding by a different air toxic in a sensitivity analysis of select two-pollutant models. To limit the

number of multiple comparisons, we evaluated 34 pollutant pairs we judged more likely to have a confounding pattern because they met two criteria: *a*) both air toxics exhibited associations with an ASD diagnosis, defined as those whose 95% CI excluded the null, and *b*) the two log-transformed air toxics were correlated in our modeling context, that is, with partial correlation at the absolute value of 0.4 or higher, after accounting for covariates (the family mean air toxics concentration, birth year, and census block group variables). We then used the same model structure (mixed logistic regression model of ASD diagnosis with confounders listed above) but including two individual participant air toxics concentrations and two family mean air toxics concentrations. To assure a valid comparison given different degrees of missing air toxics data, we refit the single-pollutant models to include only the sample available in the two-pollutant model, as needed.

Because previous reports have found the effect of some air toxics on ASD risk differed by child sex (Roberts et al. 2013), we evaluated modification by sex. Modification was evaluated for all air toxics in adjusted models for ASD diagnosis, using a Wald test of the cross-product term between the logarithm of the individual air toxic concentration and participant sex, using an alpha level of 0.10.

Results

In the full analytical sample ($n = 2,017$ with or without an ASD diagnosis), 68% of participants were white, non-Hispanic race/ethnicity and 19% were Hispanic (Table 1). Birth years were spread throughout the study period, and a preponderance of families had two or three siblings, in line with the AGRE recruitment design. SRS total t -scores exhibited a bimodal distribution consistent with

Table 1. Characteristics of included AGRE participants by ASD diagnosis, score on the Social Responsiveness Scale, and Calibrated Severity Score. [Values are n (%) or mean \pm SD].

Characteristic	ASD diagnosis ($n = 1,540$)	No ASD diagnosis ($n = 477$)	SRS total t -score ($n = 1,272$)		CSS ($n = 1,380$)	
Sex						
Male	1,210 (79)	240 (50)	895 (70)	77.0 \pm 19.9	1,093 (79)	7.5 \pm 1.9
Female	330 (21)	237 (50)	377 (30)	70.3 \pm 25.7	287 (21)	6.9 \pm 2.1
Race/ethnicity						
Non-Hispanic white	1,039 (67)	324 (68)	871 (70)	75.5 \pm 21.8	939 (68)	7.4 \pm 1.9
Non-Hispanic black	26 (2)	6 (1)	30 (2)	71.4 \pm 17.0	24 (2)	7.3 \pm 1.8
Hispanic	290 (19)	91 (19)	247 (19)	74.5 \pm 23.5	265 (19)	7.3 \pm 2.0
Other	125 (8)	30 (6)	99 (8)	73.6 \pm 21.9	114 (8)	7.1 \pm 1.9
Unknown	60 (4)	26 (5)	25 (2)	73.2 \pm 21.5	38 (3)	7.1 \pm 2.0
Number of siblings in family (n)						
1	15 (1)	0 (0)	9 (1)	81.1 \pm 12.7	13 (1)	7.8 \pm 1.4
2	556 (36)	31 (7)	401 (32)	79.4 \pm 19.5	482 (35)	7.4 \pm 1.9
3	583 (38)	197 (41)	490 (39)	74.9 \pm 22.6	533 (39)	7.3 \pm 2.0
4	210 (14)	136 (29)	225 (18)	68.9 \pm 22.8	191 (14)	7.5 \pm 2.0
5–11	176 (11)	113 (24)	147 (12)	72.4 \pm 23.2	161 (12)	7.1 \pm 2.0
Birth year						
1994–1997	439 (29)	131 (27)	351 (28)	74.4 \pm 22.9	360 (26)	7.4 \pm 2.0
1998–2000	465 (30)	119 (25)	402 (32)	74.8 \pm 22.9	436 (32)	7.1 \pm 1.9
2001–2003	424 (28)	121 (25)	368 (29)	75.1 \pm 20.9	396 (29)	7.5 \pm 2.0
2004–2007	212 (14)	106 (22)	151 (12)	76.8 \pm 19.9	188 (14)	7.5 \pm 1.7
Maternal age (y)						
Missing	50 (3)	16 (3)	46 (4)	77.7 \pm 22.0	21 (2)	6.8 \pm 2.0
17–24	231 (15)	63 (13)	209 (16)	76.5 \pm 22.1	216 (16)	7.5 \pm 1.9
25–29	448 (29)	140 (30)	377 (30)	75.6 \pm 22.5	408 (30)	7.1 \pm 2.1
30–34	520 (34)	160 (34)	397 (31)	73.3 \pm 21.3	471 (34)	7.5 \pm 1.8
≥ 35	291 (19)	98 (21)	243 (19)	75.0 \pm 22.1	264 (19)	7.4 \pm 1.9
U.S. EPA Region ^a						
1. CT ME MA NH RI (VT)	46 (3)	11 (2)	26 (2)	79.1 \pm 19.2	31 (2)	7.5 \pm 2.2
2. NJ NY	150 (10)	34 (7)	88 (7)	75.8 \pm 23.0	136 (10)	7.4 \pm 1.9
3. DE DC MD PA VA WV	141 (9)	38 (8)	110 (9)	74.9 \pm 19.2	124 (9)	7.4 \pm 1.8
4. AL FL GA KY MS NC SC (TN)	128 (8)	40 (8)	95 (7)	76.7 \pm 19.1	119 (9)	7.5 \pm 1.8
5. IL IN MI MN OH WI	237 (15)	70 (15)	194 (15)	76.8 \pm 20.9	204 (15)	7.6 \pm 1.8
6. AR LA NM OK TX	111 (7)	41 (9)	80 (6)	77.8 \pm 24.1	99 (7)	6.9 \pm 1.9
7. IA KS MO NE	65 (4)	14 (3)	55 (4)	80.7 \pm 21.4	53 (4)	7.3 \pm 2.1
8. CO UT (WY MT ND SD)	31 (2)	6 (1)	16 (1)	82.9 \pm 19.5	28 (2)	7.1 \pm 2.2
9. AZ CA (HI) NV	592 (38)	210 (44)	572 (45)	72.9 \pm 22.9	551 (40)	7.3 \pm 2.0
10. (AK) ID OR WA	39 (3)	13 (3)	36 (3)	71.3 \pm 21.8	35 (3)	8.0 \pm 1.7
Census block group percentiles						
Population density						
0–35	383 (25)	128 (27)	313 (25)	76.5 \pm 21.8	337 (24)	7.4 \pm 1.9
36–65	546 (35)	163 (34)	436 (34)	75.5 \pm 21.6	485 (35)	7.4 \pm 1.9
66–100 (highest density)	611 (40)	186 (39)	523 (41)	73.7 \pm 22.4	558 (40)	7.3 \pm 1.9
At least a high school education						
0–25	712 (46)	231 (48)	604 (47)	74.4 \pm 22.1	630 (46)	7.4 \pm 2.0
26–60	486 (32)	149 (31)	399 (31)	74.5 \pm 21.9	446 (32)	7.2 \pm 2.0
61–100 (higher education)	342 (22)	97 (20)	269 (21)	77.1 \pm 21.8	304 (22)	7.4 \pm 1.8
Median rent						
0–25	758 (49)	243 (51)	644 (51)	73.4 \pm 22.6	689 (50)	7.4 \pm 1.9
26–50	430 (28)	113 (24)	357 (28)	75.6 \pm 21.5	393 (28)	7.3 \pm 1.9
51–100 (higher rent)	352 (23)	121 (25)	271 (21)	78.0 \pm 20.8	298 (22)	7.3 \pm 2.0

Note: AGRE, Autism Genetic Resource Exchange; ASD, Autism Spectrum Disorder; CSS, Calibrated Severity Score; SRS, Social Responsiveness Scale.

^aStandard state abbreviations are used. There were no participants for states listed in parentheses.

the nature of this multiplex case-control sample. Mean SRS scores for participants with an ASD diagnosis were well above the typical cutoff of 76 used to indicate severe autism (Constantino et al. 2003) (mean \pm SD SRS total *t*-score of 84.5 ± 15.8) whereas those without an ASD diagnosis had a mean of 42.3 ± 10.9 . The mean CSS among participants with an ASD diagnosis was near the upper end of the 1–10 scale (7.4 ± 1.9), and the correlation between the SRS total *t*-score and CSS among those with ASD was low: 0.25 with a partial correlation (accounting for family structure and adjusted covariates) of 0.28. Participants with an ASD diagnosis were more commonly males, had fewer siblings, and were born in earlier years compared with unaffected siblings, but did not differ by typical risk factors for ASD such as maternal age (Table 1). The largest proportion of subjects ($\sim 40\%$) was born in U.S. EPA Region 9, which includes California.

In adjusted models of log-transformed air toxics, several air toxics exhibited positive or inverse associations with ASD diagnosis (Table 2). Controlling the FDR at 0.1, notable positive associations were for 1,4-dioxane, bromoform, dibenzofurans, glycol ethers, methyl *tert*-butyl ether (MTBE), and propionaldehyde; whereas 1,4-dichlorobenzene, 4,4'-methylene diphenyl diisocyanate (MDI), benzidine, and ethyl carbamate (urethane) were inversely associated with an ASD diagnosis. These air toxics with notable associations were distributed across five correlation groups or were not correlated with other air toxics. Some additional air toxics exhibited associations with confidence limits that did not include the null but did not pass correction for multiple comparisons. In the sensitivity analysis of restricted birth years, ASD diagnosis associations were similar or greater in magnitude, although with reduced precision due to the reduced sample size (see Table S3).

Autism phenotype as measured by the SRS total *t*-score was not notably associated with any air toxics in adjusted models after controlling for the FDR (Table 2). The other continuous outcome, autism severity measured by the CSS, was positively associated with carbon disulfide (with an estimated increase of 0.88 points on the 10-point CSS scale) and chlorobenzene (0.73 point increase), whereas less severe autism was associated with 1,4-dichlorobenzene (1.41 points lower on the CSS), after accounting for the FDR (Table 2). Patterns of associations across the three autism outcome measures were generally consistent in direction, so that above-null associations with ASD diagnosis for a given air toxic were usually found with a positive change in the SRS and CSS, and vice versa. (An exception may be 1,4-dioxane, which showed a risk association with ASD diagnosis but was associated with a lower CSS.)

Some correlation groups included air toxics with results of similar magnitude and direction. For example, Group C included positive associations with ASD diagnosis for diesel particulate matter, ethyl benzene, and xylenes (with confidence limits excluding the null but not passing FDR), with all seven air toxics in this group exhibiting null or positive associations (Table 2). Group F is another example where all four correlated air toxics had positive associations ranging in magnitude from 1.24 (4,4'-methylenedianiline) to 2.87 (1,4-dioxane). An example of a group with inverse associations is Group M including 1,2-dibromo-3-chloropropane and 4-nitrophenol, both with below-null odds ratios with confidence limits excluding the null but not passing FDR.

We found some evidence that measured air toxics acted as copollutant confounders, so that when they were included as adjustment factors in two-pollutant models, the odds ratio for the other air toxic was attenuated (Table 3). Some changes in estimate were strong. An example is 1,1,1-trichloroethane (methyl chloroform) that had a single-pollutant odds ratio for an ASD diagnosis of 1.88 (95% CI: 1.04, 3.38), which was attenuated to 0.55 (95% CI: 0.22, 1.37) adjusting for benzidine, to 0.83 (95% CI: 0.32, 2.14) adjusting for mercury compounds, and to 1.23

(95% CI: 0.48, 3.17) adjusting for pentachloronitrobenzene. Another example is diesel particulate matter that had an odds ratio with ASD diagnosis of 1.44 (95% CI: 1.06, 1.97), which was attenuated to 1.06 (95% CI: 0.73, 1.55) adjusting for propionaldehyde. In contrast, associations for the air toxics found to be notably associated with ASD diagnosis (after controlling for multiple comparisons) were robust to adjusting for correlated air toxics; in all two-pollutant models, odds ratios were generally unchanged for risk associations with MTBE and propionaldehyde, and for protective associations for 1,4-dichlorobenzene, 4,4'-methylene diphenyl diisocyanate (MDI), and benzidine. The precision for odds ratio from the two-pollutant models was only slightly worse than in single-pollutant models, despite the inclusion of correlated air toxics, the maximum partial correlation being 0.93 for xylenes and ethyl benzene.

When examining participant sex as a modifier of associations between air toxics and ASD diagnosis, associations were generally higher among males (see Table S4). We did not observe modification for those air toxics identified to have notable associations after multiple comparison correction in primary analyses. However, we did observe modification for 11 other air toxics.

Discussion

We examined 155 air toxics in relation to three autism-related endpoints, finding several air toxics associated with increased and a few with decreased risk of ASD diagnosis and autism severity, after adjusting for the family propensity to be exposed to air toxics and correcting for the possibility of false positives due to multiple comparisons.

Our results are consistent with other lines of evidence that traffic-related air pollutants are linked to ASD. Two of the air toxics with stronger risk associations here (considered notable after accounting for multiple comparisons) are part of the air pollution mixture emitted from vehicles: propionaldehyde and MTBE. Propionaldehyde is formed from the combustion of gasoline, diesel, and waste/biomass burning, and also has industrial uses. Human or animal impacts of low-level inhaled propionaldehyde are not well-studied (U.S. EPA 2017). MTBE was a widely used gasoline additive phased out in the mid-2000s, toward the end of the exposure period included here. Although the mechanisms whereby MTBE may have an impact on autism are unknown, nervous system involvement is supported by evidence that MTBE is a central nervous system depressant in adult humans, and by rodent studies that implicate neurotransmitter alterations and impacts on spatial memory (Kinawy et al. 2014; ATSDR 1996; Zheng et al. 2009). We also found positive associations between other traffic-related air toxics and ASD, but only at a more liberal statistical significance threshold ($p < 0.05$): diesel particulate matter, ethyl benzene, and xylenes. That these air toxics clustered together (correlation group C) suggests that they arose from a shared source, perhaps vehicular traffic. These results for diesel particulate matter, ethylbenzene, and xylenes were consistent with some, but not all, previous studies (see Table S1). For two other traffic-related air toxics—benzene and toluene—previous studies found a link with ASD, but our results were null. Discrepancies between our findings and those in prior reports may be due in part to our analytical design, which controlled for the family-level exposure (as discussed below), or could be influenced by copollutant confounding. Our findings regarding the traffic pollutants MTBE and propionaldehyde, together with the preponderance of published associations between traffic-related air toxics and also PM_{2.5} with ASD risk (Becerra et al. 2013; Volk et al. 2013; Lam et al. 2016), further support a role for mobile source emissions in ASD.

Table 2. Adjusted associations between log-transformed air toxics and ASD diagnosis, Social Responsiveness Scale total *t*-score, and autism Calibrated Severity Score, by air toxics correlation group.

Air Toxic	ASD diagnosis OR (95% CI)	Change in SRS score (95% CI)	Change in CSS (95% CI)
Group A			
1,4-Dichlorobenzene (<i>p</i> -dichlorobenzene) ^a	0.25 (0.09, 0.66) ^b	−15.24 (−25.12, −5.36)	−1.41 (−2.28, −0.54) ^b
Bis(2-ethylhexyl)phthalate	6.62 (0.35, 124.22)	2.90 (−28.68, 34.47)	−1.03 (−3.60, 1.54)
Bromoform	3.94 (1.68, 9.21) ^b	3.35 (−6.89, 13.59)	0.79 (−0.05, 1.62)
Captan	1.08 (0.56, 2.06)	−4.63 (−12.37, 3.11)	−0.20 (−0.83, 0.42)
Carbaryl	1.15 (0.60, 2.22)	−5.58 (−13.22, 2.05)	−0.13 (−0.78, 0.51)
Carbon tetrachloride ^{a,c}	1.52 (0.55, 4.19)	8.16 (−3.91, 20.23)	−0.26 (−1.24, 0.72)
Chlordane	0.91 (0.17, 4.76)	−0.30 (−20.13, 19.53)	0.34 (−1.61, 2.29)
Hexachloroethane	1.45 (0.49, 4.30)	0.52 (−12.48, 13.52)	0.75 (−0.32, 1.83)
Methyl ethyl ketone (2-butanone)	1.30 (0.49, 3.44)	7.76 (−4.98, 20.5)	−1.13 (−2.19, −0.07)
Group B			
2,4-Dinitrotoluene	0.99 (0.87, 1.13)	−0.37 (−1.92, 1.18)	0.07 (−0.06, 0.20)
Cyanide compounds	1.04 (0.88, 1.22)	−0.19 (−2.08, 1.71)	0.13 (−0.03, 0.30)
Dimethyl sulfate	1.11 (0.85, 1.43)	−0.18 (−3.21, 2.85)	0.13 (−0.12, 0.37)
N,N-Dimethyl aniline	1.01 (0.88, 1.15)	−0.18 (−1.78, 1.41)	0.07 (−0.06, 0.20)
Group C			
Diesel particulate matter ^c	1.44 (1.06, 1.97)	3.23 (−0.33, 6.79)	0.00 (−0.33, 0.32)
Ethyl benzene ^c	1.55 (1.08, 2.23)	2.86 (−1.25, 6.96)	0.12 (−0.25, 0.49)
Hexane ^c	1.30 (0.89, 1.91)	2.08 (−2.17, 6.33)	0.12 (−0.26, 0.51)
Methanol	0.99 (0.67, 1.45)	1.97 (−2.23, 6.16)	0.21 (−0.17, 0.60)
Naphthalene	0.96 (0.56, 1.65)	3.51 (−2.31, 9.34)	0.20 (−0.32, 0.72)
Toluene ^c	1.05 (0.71, 1.55)	1.58 (−2.99, 6.14)	−0.11 (−0.49, 0.28)
Xylenes (isomers and mixture) ^c	1.49 (1.04, 2.14)	3.38 (−0.76, 7.52)	0.14 (−0.23, 0.50)
Group D			
1,3-Butadiene ^c	0.98 (0.73, 1.32)	0.94 (−2.40, 4.27)	0.10 (−0.19, 0.39)
2,2,4-Trimethylpentane	1.79 (1.12, 2.87)	5.49 (0.54, 10.43)	0.20 (−0.25, 0.66)
Benzene ^c	1.13 (0.81, 1.57)	3.33 (−0.77, 7.43)	0.00 (−0.32, 0.33)
Group E			
Carbon disulfide	1.46 (0.85, 2.53)	4.10 (−2.57, 10.77)	0.88 (0.34, 1.41) ^b
Mercury compounds ^c	1.78 (1.11, 2.84)	3.83 (−1.83, 9.50)	0.26 (−0.21, 0.73)
Vinyl chloride ^c	1.44 (0.94, 2.23)	1.02 (−4.06, 6.11)	0.22 (−0.21, 0.66)
Group F			
1,1,1-Trichloroethane (methyl chloroform)	1.88 (1.04, 3.38)	3.73 (−2.91, 10.37)	0.20 (−0.35, 0.76)
1,4-Dioxane	2.87 (1.43, 5.76) ^b	4.36 (−3.53, 12.24)	−0.42 (−1.11, 0.26)
4,4'-Methylenedianiline	1.24 (0.67, 2.27)	−0.97 (−7.99, 6.05)	−0.08 (−0.67, 0.51)
Pentachloronitrobenzene	2.22 (1.23, 4.04)	3.31 (−3.41, 10.03)	−0.33 (−0.89, 0.22)
Group G			
1,1,2,2-Tetrachloroethane ^c	1.37 (0.94, 1.98)	−1.10 (−5.3, 3.11)	−0.13 (−0.53, 0.27)
Ethylene dibromide (dibromomethane) ^c	0.97 (0.54, 1.74)	−3.74 (−10.12, 2.65)	−0.01 (−0.58, 0.55)
Ethylene dichloride ^c	1.37 (0.97, 1.93)	0.89 (−3.14, 4.93)	0.04 (−0.31, 0.38)
Propylene dichloride ^c	1.58 (1.04, 2.41)	−0.67 (−5.49, 4.16)	−0.02 (−0.45, 0.41)
Group H			
1,1-Dimethyl hydrazine	1.51 (0.82, 2.78)	0.38 (−6.21, 6.97)	−0.39 (−0.95, 0.18)
3,3-Dichlorobenzidine	1.04 (0.59, 1.84)	−3.20 (−9.35, 2.95)	−0.69 (−1.23, −0.16)
4,6-Dinitro- <i>o</i> -cresol, and salts	1.07 (0.63, 1.83)	−0.42 (−6.96, 6.12)	−0.22 (−0.76, 0.33)
<i>o</i> -Anisidine	2.13 (1.11, 4.06)	1.73 (−5.16, 8.62)	−0.23 (−0.82, 0.36)
Benzotrithloride	1.03 (0.48, 2.22)	−3.35 (−11.48, 4.77)	−0.59 (−1.28, 0.09)
Bis(chloromethyl)ether	0.89 (0.42, 1.86)	−5.56 (−13.03, 2.18)	−0.23 (−0.93, 0.48)
Chloromethyl methyl ether	1.15 (0.59, 2.24)	−3.47 (−10.84, 3.90)	−0.41 (−1.02, 0.20)
Dichloroethyl ether [bis(2-chloroethyl) ether]	1.18 (0.63, 2.18)	0.14 (−7.68, 7.96)	−0.51 (−1.11, 0.09)
Dichlorvos	1.19 (0.56, 2.51)	−2.65 (−10.51, 5.21)	−0.03 (−0.69, 0.64)
Diethyl sulfate	1.22 (0.63, 2.37)	0.98 (−6.75, 8.71)	−0.27 (−0.90, 0.36)
Heptachlor	1.64 (0.83, 3.23)	1.90 (−5.37, 9.17)	−0.41 (−1.00, 0.18)
Methyl isocyanate	1.99 (1.06, 3.75)	2.21 (−4.52, 8.94)	−0.24 (−0.81, 0.33)
Phosgene	1.27 (0.70, 2.32)	−1.53 (−8.49, 5.44)	−0.10 (−0.67, 0.48)
<i>p</i> -Phenylenediamine	1.50 (0.83, 2.74)	2.23 (−4.91, 9.37)	−0.28 (−0.85, 0.28)
Styrene oxide	1.24 (0.52, 2.93)	−1.13 (−9.63, 7.37)	−0.52 (−1.27, 0.23)
Vinyl bromide	1.00 (0.42, 2.39)	−4.50 (−13.08, 4.08)	−0.73 (−1.51, 0.04)
Group I			
Acetaldehyde ^c	0.83 (0.61, 1.15)	1.91 (−1.98, 5.81)	−0.11 (−0.43, 0.21)
Formaldehyde ^c	1.00 (0.73, 1.36)	4.33 (0.48, 8.17)	−0.15 (−0.46, 0.17)
Methylene chloride (dichloromethane) ^c	1.09 (0.80, 1.49)	2.93 (−0.78, 6.64)	−0.05 (−0.36, 0.26)
Group J			
Acrolein ^c	1.65 (1.11, 2.43)	2.87 (−1.58, 7.31)	0.10 (−0.29, 0.49)
Cresols/cresylic acid (isomers and mixture)	1.42 (0.78, 2.57)	2.14 (−4.44, 8.73)	0.29 (−0.28, 0.85)
Propionaldehyde ^c	1.92 (1.33, 2.77) ^b	2.65 (−1.46, 6.77)	0.19 (−0.18, 0.56)
Group K			
Aniline	1.22 (0.68, 2.21)	1.01 (−5.81, 7.84)	−0.16 (−0.73, 0.42)
Chloroacetic acid	1.47 (0.84, 2.57)	0.67 (−5.59, 6.93)	0.08 (−0.44, 0.60)
Titanium tetrachloride	1.43 (0.79, 2.59)	2.77 (−3.81, 9.34)	−0.25 (−0.81, 0.30)

Table 2. (Continued.)

Air Toxic	ASD diagnosis OR (95% CI)	Change in SRS score (95% CI)	Change in CSS (95% CI)
Group L			
1,2,4-Trichlorobenzene	1.28 (0.98, 1.66)	0.82 (−2.22, 3.85)	0.32 (0.06, 0.58)
<i>o</i> -Toluidine	1.46 (1.09, 1.97)	1.22 (−2.22, 4.65)	0.16 (−0.13, 0.45)
Group M			
1,2-Dibromo-3-chloropropane	0.60 (0.37, 0.97)	−5.35 (−11.01, 0.31)	−0.28 (−0.73, 0.17)
4-Nitrophenol	0.50 (0.30, 0.84)	−7.35 (−12.96, −1.75)	−0.37 (−0.86, 0.11)
Group N			
2,4-Dinitrophenol	1.49 (0.93, 2.38)	0.00 (−5.36, 5.36)	0.22 (−0.23, 0.67)
Dibenzofurans	2.53 (1.35, 4.74) ^b	4.83 (−2.33, 11.99)	0.39 (−0.23, 1.00)
Group O			
2-Chloroacetophenone	0.80 (0.41, 1.58)	−3.59 (−11.62, 4.43)	−0.29 (−0.91, 0.33)
Methyl hydrazine	1.10 (0.51, 2.39)	−2.87 (−12.00, 6.26)	−0.22 (−0.96, 0.53)
Group P			
2-Nitropropane	1.17 (0.95, 1.43)	1.35 (−0.98, 3.67)	0.26 (0.07, 0.45)
Nitrobenzene	1.09 (0.98, 1.23)	0.19 (−1.18, 1.56)	0.09 (−0.02, 0.20)
Group Q			
4,4'-Methylene diphenyl diisocyanate (MDI)	0.54 (0.39, 0.76) ^b	−5.51 (−8.86, −2.17)	−0.19 (−0.49, 0.10)
Ethylene glycol	0.61 (0.37, 1.00)	−2.38 (−7.98, 3.21)	−0.09 (−0.59, 0.40)
Group R			
Acetonitrile	1.05 (0.83, 1.33)	0.57 (−2.13, 3.26)	0.12 (−0.11, 0.35)
Allyl chloride	1.03 (0.91, 1.17)	0.27 (−1.17, 1.72)	0.14 (0.02, 0.26)
Group S			
Antimony compounds	1.13 (0.74, 1.74)	−0.56 (−5.34, 4.22)	0.09 (−0.33, 0.52)
Cobalt compounds	1.12 (0.77, 1.61)	0.55 (−3.60, 4.70)	0.22 (−0.14, 0.59)
Group T			
Chlorobenzene	1.35 (0.86, 2.14)	5.51 (0.17, 10.85)	0.73 (0.30, 1.15) ^b
Methyl bromide (bromomethane)	1.08 (0.65, 1.79)	3.42 (−2.69, 9.53)	0.47 (−0.02, 0.96)
Group U			
Chromium compounds ^c	1.00 (0.74, 1.35)	0.44 (−3.07, 3.94)	−0.26 (−0.56, 0.04)
Nickel compounds ^c	1.08 (0.77, 1.51)	−1.09 (−5.31, 3.12)	−0.20 (−0.54, 0.13)
Group V			
Dimethyl formamide	1.18 (0.98, 1.43)	−0.10 (−2.18, 1.98)	0.08 (−0.10, 0.26)
Ethyl chloride	1.06 (0.80, 1.39)	−1.01 (−4.11, 2.10)	0.23 (−0.04, 0.49)
Group W			
Epichlorohydrin	1.25 (0.96, 1.64)	0.65 (−2.43, 3.73)	−0.01 (−0.28, 0.26)
Ethyl acrylate	1.28 (0.93, 1.75)	0.51 (−3.07, 4.10)	0.17 (−0.14, 0.48)
Group X			
Hexachlorobutadiene	1.28 (0.89, 1.84)	4.28 (−0.23, 8.78)	0.50 (0.14, 0.85)
Hexachlorocyclopentadiene	1.06 (0.94, 1.18)	0.57 (−0.78, 1.92)	0.04 (−0.07, 0.15)
Group Y			
Hydrochloric acid	1.16 (0.78, 1.73)	1.52 (−3.11, 6.15)	0.10 (−0.31, 0.51)
Hydrofluoric acid	1.24 (0.89, 1.73)	−0.36 (−4.12, 3.40)	−0.18 (−0.53, 0.16)
Group Z			
Maleic anhydride	1.82 (0.90, 3.72)	−0.15 (−8.26, 7.96)	−0.16 (−0.88, 0.56)
Phthalic anhydride	0.89 (0.41, 1.91)	−5.24 (−13.80, 3.33)	−0.31 (−1.08, 0.46)
Air toxics not in a group			
1,1,2-Trichloroethane	1.10 (0.79, 1.53)	−1.27 (−5.13, 2.58)	0.35 (0.03, 0.67)
1,2-Epoxybutane	0.67 (0.38, 1.19)	−3.21 (−9.60, 3.19)	−0.61 (−1.17, −0.05)
1,2-Propylenimine	1.19 (0.69, 2.06)	−0.19 (−6.65, 6.28)	−0.03 (−0.56, 0.50)
1,3-Dichloropropene ^c	1.00 (0.95, 1.05)	0.20 (−0.44, 0.84)	0.02 (−0.03, 0.07)
2,4,6-Trichlorophenol	1.64 (0.57, 4.70)	0.21 (−12.30, 12.72)	0.13 (−0.85, 1.11)
2,4-D, salts and esters	1.40 (0.71, 2.78)	−2.73 (−10.85, 5.38)	0.02 (−0.65, 0.69)
2,4-Toluene diisocyanate	1.64 (1.11, 2.44)	2.15 (−2.14, 6.44)	−0.19 (−0.56, 0.18)
4,4'-Methylene bis(2-chloroaniline)	1.93 (0.66, 5.64)	3.61 (−7.81, 15.04)	−0.34 (−1.34, 0.66)
Acetamide	1.02 (0.52, 2.01)	2.46 (−5.57, 10.49)	0.76 (0.10, 1.42)
Acetophenone	1.12 (0.75, 1.68)	3.74 (−0.75, 8.22)	−0.21 (−0.61, 0.18)
Acrylamide	1.47 (0.82, 2.63)	2.72 (−3.87, 9.31)	0.18 (−0.38, 0.73)
Acrylic acid	1.39 (0.89, 2.15)	1.37 (−3.57, 6.31)	0.19 (−0.23, 0.61)
Acrylonitrile ^c	0.97 (0.66, 1.42)	−1.97 (−6.59, 2.66)	−0.09 (−0.47, 0.28)
Arsenic compounds ^c	0.94 (0.68, 1.30)	0.93 (−2.68, 4.54)	−0.11 (−0.42, 0.20)
Asbestos ^d	7.02 (0.32, 151.73)	22.68 (−8.75, 54.1)	−3.52 (−6.93, −0.11)
Benzidine	0.41 (0.25, 0.68) ^b	−8.03 (−13.53, −2.52)	−0.50 (−0.96, −0.04)
Benzyl chloride	1.12 (0.74, 1.68)	0.39 (−4.22, 5.00)	−0.02 (−0.44, 0.40)
Beryllium compounds ^c	0.74 (0.55, 1.02)	−0.88 (−4.39, 2.62)	−0.30 (−0.61, 0.01)
Biphenyl	0.88 (0.57, 1.35)	−0.97 (−5.57, 3.62)	0.05 (−0.35, 0.46)
Cadmium compounds ^c	0.93 (0.70, 1.24)	0.12 (−3.17, 3.41)	−0.19 (−0.47, 0.09)
Carbonyl sulfide	1.29 (0.80, 2.10)	−3.88 (−9.35, 1.58)	0.06 (−0.40, 0.52)
Catechol	0.95 (0.58, 1.56)	0.57 (−5.14, 6.28)	0.24 (−0.25, 0.72)
Chlorine	1.22 (0.78, 1.91)	0.25 (−4.54, 5.05)	0.03 (−0.42, 0.49)
Chlorobenzilate	0.78 (0.25, 2.39)	−1.43 (−15.86, 13.00)	−0.25 (−1.12, 0.62)
Chloroform ^c	1.01 (0.62, 1.64)	2.42 (−3.28, 8.12)	0.13 (−0.34, 0.61)

Table 2. (Continued.)

Air Toxic	ASD diagnosis OR (95% CI)	Change in SRS score (95% CI)	Change in CSS (95% CI)
Chloroprene	1.11 (0.99, 1.26)	0.28 (−1.13, 1.70)	0.07 (−0.05, 0.19)
Coke oven emissions ^c	0.70 (0.22, 2.23)	−14.59 (−26.8, −2.37)	0.32 (−0.81, 1.45)
Cumene	0.73 (0.47, 1.14)	−3.78 (−8.72, 1.16)	0.19 (−0.26, 0.64)
Dibutylphthalate	1.08 (0.77, 1.50)	−0.89 (−4.67, 2.90)	−0.10 (−0.43, 0.23)
Diethanolamine	1.19 (0.86, 1.65)	0.01 (−3.60, 3.62)	0.08 (−0.24, 0.40)
Dimethyl phthalate	0.76 (0.57, 1.00)	−2.81 (−6.01, 0.40)	−0.19 (−0.47, 0.08)
Ethyl carbamate (Urethane)	0.30 (0.16, 0.57) ^b	−9.84 (−16.78, −2.91)	−0.61 (−1.21, 0.00)
Ethylene oxide ^c	0.85 (0.62, 1.18)	−2.70 (−6.56, 1.16)	−0.17 (−0.50, 0.16)
Ethylene thiourea	6.33 (1.50, 26.66)	4.75 (−11.55, 21.06)	0.03 (−1.34, 1.40)
Ethylidene dichloride (1,1-dichloroethane)	0.62 (0.43, 0.89)	−4.46 (−8.58, −0.34)	0.18 (−0.15, 0.50)
Glycol ethers	2.05 (1.39, 3.02) ^b	3.52 (−0.97, 8.01)	0.20 (−0.19, 0.59)
Hexachlorobenzene ^c	1.08 (0.90, 1.30)	−0.80 (−3.06, 1.45)	0.07 (−0.11, 0.26)
Hexamethylene-1,6-diisocyanate	0.65 (0.39, 1.09)	−3.89 (−9.56, 1.77)	−0.40 (−0.91, 0.10)
Hydrazine ^c	0.90 (0.67, 1.21)	−1.72 (−5.21, 1.77)	−0.33 (−0.62, −0.04)
Hydroquinone	1.52 (0.76, 3.03)	0.22 (−8.11, 8.55)	−0.29 (−0.97, 0.39)
Isophorone	1.24 (1.03, 1.50)	1.53 (−0.58, 3.63)	0.21 (0.03, 0.39)
Lead compounds ^c	1.17 (0.89, 1.53)	0.85 (−2.12, 3.82)	−0.07 (−0.33, 0.18)
Manganese compounds ^c	0.75 (0.60, 0.95)	−1.79 (−4.48, 0.90)	−0.14 (−0.37, 0.09)
Methyl iodide (iodomethane)	1.32 (0.72, 2.41)	0.08 (−7.03, 7.19)	0.13 (−0.46, 0.73)
Methyl isobutyl ketone	0.84 (0.54, 1.31)	1.32 (−3.56, 6.20)	−0.01 (−0.45, 0.43)
Methyl methacrylate	1.31 (0.84, 2.05)	2.28 (−2.67, 7.24)	0.46 (0.04, 0.89)
Methyl <i>tert</i> -butyl ether (MTBE) ^c	2.33 (1.31, 4.15) ^b	5.88 (−0.60, 12.36)	0.07 (−0.54, 0.68)
Nitrosodimethylamine	0.42 (0.11, 1.53)	−4.80 (−21.73, 12.14)	−0.53 (−1.77, 0.71)
Pentachlorophenol	0.71 (0.30, 1.71)	−4.73 (−15.05, 5.60)	−0.32 (−1.16, 0.52)
Phenol	0.79 (0.51, 1.23)	−1.50 (−6.42, 3.42)	−0.32 (−0.75, 0.12)
Phosphine	1.74 (0.92, 3.29)	0.37 (−7.00, 7.74)	0.02 (−0.63, 0.67)
Phosphorous ^c	0.67 (0.24, 1.82)	−3.33 (−14.95, 8.28)	0.39 (−0.62, 1.40)
Polychlorinated biphenyls (PCBs) ^c	1.42 (1.00, 2.00)	−0.07 (−4.31, 4.17)	0.23 (−0.13, 0.59)
Polycyclic aromatic hydrocarbons (PAHs) ^c	0.77 (0.54, 1.11)	−5.54 (−9.80, −1.29)	−0.01 (−0.37, 0.35)
Polycyclic organic matter (POM) ^f	0.95 (0.63, 1.42)	0.64 (−3.76, 5.04)	−0.28 (−0.65, 0.10)
Propylene oxide	1.08 (0.89, 1.30)	−0.68 (−2.77, 1.40)	0.18 (−0.02, 0.39)
Quinoline ^c	0.81 (0.68, 0.96)	−1.62 (−3.69, 0.46)	−0.12 (−0.30, 0.05)
Quinone (<i>p</i> -benzoquinone)	1.37 (0.77, 2.43)	2.64 (−3.85, 9.14)	0.06 (−0.50, 0.61)
Selenium compounds	1.08 (0.72, 1.60)	−0.12 (−4.41, 4.17)	−0.10 (−0.51, 0.30)
Styrene ^c	1.16 (0.83, 1.62)	5.02 (1.15, 8.89)	0.03 (−0.31, 0.36)
Tetrachloroethylene (perchloroethylene) ^c	0.90 (0.67, 1.19)	−0.29 (−3.40, 2.83)	−0.24 (−0.55, 0.07)
Trichloroethylene ^c	1.18 (0.86, 1.61)	2.05 (−1.66, 5.77)	0.14 (−0.17, 0.44)
Triethylamine	1.25 (0.86, 1.81)	1.39 (−2.67, 5.46)	0.13 (−0.23, 0.49)
Trifluralin	1.30 (0.69, 2.46)	−0.88 (−8.44, 6.68)	0.40 (−0.22, 1.01)
Vinyl acetate	0.88 (0.55, 1.40)	−1.25 (−6.56, 4.06)	−0.08 (−0.55, 0.40)
Vinylidene chloride (1,1-dichloroethylene)	1.17 (0.80, 1.72)	1.63 (−2.72, 5.98)	0.27 (−0.09, 0.62)

Note: All models include the single log-transformed air toxic, contrasting the levels of air toxics listed in Table S2 (usually 75% vs. 25%), with a random effect for family, and adjust for the mean air toxic level in the family, birth year, and the census block group population density, education level, and median rent. Unless otherwise specified, sample sizes for a given air toxic reflect inclusion in three NATA model years (1999, 2002, and 2005): 1,101 cases and 346 controls (among 780 families), 921 individuals with an SRS (among 543 families), and 1,020 cases with a CSS (among 660 families). ASD, Autism Spectrum Disorder; CI, confidence interval; CSS, Calibrated Severity Score; M, mean; NATA, National-scale Air Toxics Assessment; OR, odds ratio; SD, standard deviation; SRS, Social Responsiveness Scale.

^a1,4-Dichlorobenzene and carbon tetrachloride had inverse correlations with the other air toxics in Group A. All other correlations in all groups were positive.

^bStatistically significantly different from the null after correcting for multiple comparisons using the false discovery rate (set at 0.1).

^cSample size for these air toxics reflects inclusion in all four NATA model years: 1,540 cases and 477 controls (among 1,006 families), 1,272 individuals with an SRS (among 678 families), and 1,380 cases with a CSS (among 845 families).

^dAsbestos was only included in the 1999 NATA model year, allowing sample sizes of 465 cases and 119 controls (among 456 families), 402 individuals with an SRS (among 309 families), and 436 cases with a CSS (among 357 families).

^ePhosphorous was included in NATA 2002 and 2005 model years, allowing sample sizes of 636 cases and 227 controls (among 536 families), 519 individuals with an SRS (among 335 families), and 584 cases with a CSS (among 414 families).

^fPOM was included in the NATA 1996 and 1999 model years, allowing sample sizes of 904 cases and 250 controls (among 729 families), 753 individuals with an SRS (among 468 families), and 796 cases with a CSS (among 562 families).

It would be ideal to identify the individual chemical species within the traffic pollution mixture responsible for increased ASD risk. This is difficult because these exposures occur together, confounding observational associations of a single pollutant, a problem of copollutant confounding that is common in environmental epidemiology. Disentangling the role of individual chemicals (i.e., confounding) and whether combinations of chemicals may act in new ways (i.e., interaction) are among the key questions of environmental mixtures currently being addressed (Braun et al. 2016). We partly addressed the question of copollutant confounding by examining select two-pollutant models with the purpose of clarifying our main results. Approaches like this that reduce data complexity and focus on specific questions are in alignment with current recommendations for mixtures studies

(Taylor et al. 2016). In these sensitivity analyses we did find evidence for copollutant confounding. For example, positive associations of propionaldehyde with ASD persisted following adjustment for traffic-related air toxics like acrolein, ethyl benzene, xylenes, and diesel particulate matter. In addition, associations of these copollutants were substantially attenuated in the two-pollutant models, suggesting that the correlation with propionaldehyde accounted for their observed effects. Associations with MTBE were also robust to adjustment for diesel particulate matter and xylenes. These confounding patterns suggest that propionaldehyde and MTBE are more likely to be related to ASD risk than the other studied traffic-related pollutants. However, conclusions regarding effects of propionaldehyde and MTBE need to be considered in the context of exposure measurement error and a model

Table 3. Adjusted associations between air toxics and ASD diagnosis comparing one-pollutant and two-pollutant models.

Pollutant A	aOR (95% CI) for pollutant A			Change in estimate ^b	A–B correlation ^c	Pollutant B	aOR (95% CI) for pollutant B			Change in estimate ^b
	Single-pollutant	Two-pollutant ^a (adjusted for B)	Two-pollutant ^a (adjusted for A)				Single-pollutant	Two-pollutant ^a (adjusted for A)	Two-pollutant ^a (adjusted for B)	
1.1.1.1-Trichloroethane (methyl chloroform)	1.88 (1.04, 3.38)	0.55 (0.22, 1.37)	0.41 (0.25, 0.68)	–123%	–0.43	Benzidine ^d	0.41 (0.25, 0.68)	0.31 (0.15, 0.64)	–30%	
1.1.1.1-Trichloroethane (methyl chloroform)	1.88 (1.04, 3.38)	0.83 (0.32, 2.14)	1.72 (0.96, 3.07)	–82%	0.47	Mercury compounds	1.72 (0.96, 3.07)	1.94 (0.84, 4.49)	12%	
1.1.1.1-Trichloroethane (methyl chloroform)	1.88 (1.04, 3.38)	1.23 (0.48, 3.17)	2.22 (1.23, 4.04)	–42%	0.41	Pentachloronitrobenzene	2.22 (1.23, 4.04)	1.80 (0.69, 4.69)	–21%	
1.2-Dibromo-3-chloropropane	0.60 (0.37, 0.97)	1.51 (0.69, 3.29)	0.41 (0.25, 0.68)	92%	0.43	Benzidine ^d	0.41 (0.25, 0.68)	0.31 (0.14, 0.69)	–27%	
1.2-Dibromo-3-chloropropane	0.60 (0.37, 0.97)	0.69 (0.42, 1.14)	0.62 (0.43, 0.89)	13%	0.42	Ethylidene dichloride (1,1-dichloroethane)	0.62 (0.43, 0.89)	0.68 (0.47, 1.00)	10%	
1.4-Dichlorobenzene (<i>p</i> -dichlorobenzene) ^d	0.25 (0.09, 0.66)	0.22 (0.05, 1.03)	0.50 (0.30, 0.84)	–13%	0.69	4-Nitrophenol	0.50 (0.30, 0.84)	1.11 (0.40, 3.08)	79%	
1.4-Dichlorobenzene (<i>p</i> -dichlorobenzene) ^d	0.25 (0.09, 0.66)	0.70 (0.15, 3.25)	0.41 (0.25, 0.68)	104%	0.67	Benzidine ^d	0.41 (0.25, 0.68)	0.32 (0.13, 0.81)	–24%	
1.4-Dichlorobenzene (<i>p</i> -dichlorobenzene) ^d	0.25 (0.09, 0.66)	0.49 (0.16, 1.52)	0.60 (0.46, 0.78)	68%	0.48	Quinoline	0.60 (0.46, 0.78)	0.64 (0.46, 0.90)	7%	
2.2.4-Trimethylpentane	1.79 (1.12, 2.87)	1.23 (0.71, 2.15)	2.14 (1.34, 3.39)	–38%	0.45	Acrolein	2.14 (1.34, 3.39)	1.89 (1.09, 3.28)	–12%	
2.2.4-Trimethylpentane	1.79 (1.12, 2.87)	1.33 (0.71, 2.46)	1.55 (1.10, 2.18)	–30%	0.56	Diesel particulate matter	1.55 (1.10, 2.18)	1.36 (0.87, 2.12)	–13%	
2.2.4-Trimethylpentane	1.79 (1.12, 2.87)	0.60 (0.24, 1.53)	2.12 (1.41, 3.18)	–109%	0.82	Ethyl benzene	2.12 (1.41, 3.18)	2.97 (1.30, 6.77)	34%	
2.2.4-Trimethylpentane	1.79 (1.12, 2.87)	0.73 (0.37, 1.44)	2.35 (1.50, 3.67)	–90%	0.68	Propionaldehyde ^d	2.35 (1.50, 3.67)	2.76 (1.46, 5.25)	16%	
2.2.4-Trimethylpentane	1.79 (1.12, 2.87)	1.13 (0.52, 2.46)	1.81 (1.21, 2.71)	–46%	0.74	Xylenes	1.81 (1.21, 2.71)	1.57 (0.80, 3.06)	–15%	
4,4'-Methylene diphenyl diisocyanate (MDI) ^d	0.54 (0.39, 0.76)	0.51 (0.35, 0.74)	0.83 (0.64, 1.07)	–6%	0.44	Manganese compounds	0.83 (0.64, 1.07)	1.05 (0.78, 1.39)	23%	
Acrolein	1.65 (1.11, 2.43)	1.44 (0.87, 2.40)	1.55 (1.08, 2.23)	–13%	0.52	Ethyl benzene	1.55 (1.08, 2.23)	1.23 (0.77, 1.98)	–23%	
Acrolein	1.65 (1.11, 2.43)	1.02 (0.61, 1.71)	1.92 (1.33, 2.77)	–48%	0.59	Propionaldehyde ^d	1.92 (1.33, 2.77)	1.83 (1.13, 2.97)	–5%	
Acrolein	1.65 (1.11, 2.43)	1.49 (0.90, 2.47)	1.49 (1.04, 2.14)	–10%	0.52	Xylenes	1.49 (1.04, 2.14)	1.18 (0.74, 1.87)	–24%	
<i>o</i> -Anisidine	2.13 (1.11, 4.06)	2.03 (0.62, 6.71)	1.99 (1.06, 3.75)	–5%	0.62	Methyl isocyanate	1.99 (1.06, 3.75)	1.09 (0.34, 3.48)	–60%	
<i>o</i> -Anisidine	2.13 (1.11, 4.06)	1.48 (0.45, 4.91)	2.22 (1.23, 4.04)	–36%	0.62	Pentachloronitrobenzene	2.22 (1.23, 4.04)	1.55 (0.44, 5.40)	–36%	
Benzidine ^d	0.41 (0.25, 0.68)	0.29 (0.13, 0.64)	2.22 (1.23, 4.04)	–35%	–0.48	Pentachloronitrobenzene	2.22 (1.23, 4.04)	0.58 (0.21, 1.60)	–134%	
Bromoforn	3.94 (1.68, 9.21)	3.36 (1.26, 8.96)	1.24 (1.03, 1.50)	–16%	0.42	Isophorone	1.24 (1.03, 1.50)	1.15 (0.91, 1.44)	–8%	
Diesel particulate matter	1.44 (1.06, 1.97)	1.30 (0.85, 1.98)	1.55 (1.08, 2.23)	–11%	0.60	Ethyl benzene	1.55 (1.08, 2.23)	1.28 (0.77, 2.11)	–19%	
Diesel particulate matter	1.44 (1.06, 1.97)	1.06 (0.73, 1.55)	1.92 (1.33, 2.77)	–31%	0.44	Propionaldehyde ^d	1.92 (1.33, 2.77)	1.93 (1.24, 2.99)	0%	
Diesel particulate matter	1.44 (1.06, 1.97)	1.33 (0.88, 2.01)	1.49 (1.04, 2.14)	–8%	0.57	Xylenes	1.49 (1.04, 2.14)	1.21 (0.75, 1.97)	–21%	
Ethyl carbamate (urethane) ^d	0.30 (0.16, 0.57)	0.18 (0.07, 0.45)	6.33 (1.5, 26.66)	–52%	0.58	Ethylene thiourea	6.33 (1.5, 26.66)	13.42 (2.76, 65.21)	75%	
Ethyl benzene	1.55 (1.08, 2.23)	1.21 (0.78, 1.87)	2.33 (1.31, 4.15)	–24%	0.46	Methyl <i>tert</i> -butyl ether ^d	2.33 (1.31, 4.15)	2.03 (1.02, 4.05)	–14%	
Ethyl benzene	1.55 (1.08, 2.23)	0.92 (0.56, 1.53)	1.92 (1.33, 2.77)	–52%	0.65	Propionaldehyde ^d	1.92 (1.33, 2.77)	1.90 (1.15, 3.13)	–1%	
Ethyl benzene	1.55 (1.08, 2.23)	1.70 (0.61, 4.73)	1.49 (1.04, 2.14)	9%	0.93	Xylenes	1.49 (1.04, 2.14)	0.91 (0.33, 2.50)	–50%	
Isophorone	1.24 (1.03, 1.50)	1.14 (0.92, 1.42)	1.46 (1.09, 1.97)	–9%	0.45	<i>o</i> -Toluidine	1.46 (1.09, 1.97)	1.33 (0.95, 1.87)	–10%	
Isophorone	1.24 (1.03, 1.50)	1.26 (1.03, 1.56)	1.04 (0.87, 1.26)	2%	0.44	Polychlorinated biphenyls (PCBs)	1.04 (0.87, 1.26)	0.98 (0.80, 1.20)	–6%	
Methyl isocyanate	1.99 (1.06, 3.75)	1.25 (0.48, 3.22)	2.22 (1.23, 4.04)	–47%	0.44	Pentachloronitrobenzene	2.22 (1.23, 4.04)	1.94 (0.70, 5.40)	–13%	
Methyl <i>tert</i> -butyl ether ^d	2.33 (1.31, 4.15)	2.10 (1.03, 4.27)	1.49 (1.04, 2.14)	–11%	0.50	Xylenes	1.49 (1.04, 2.14)	1.14 (0.73, 1.78)	–27%	
<i>o</i> -Toluidine	1.46 (1.09, 1.97)	1.51 (1.09, 2.10)	1.04 (0.87, 1.26)	3%	0.46	Polychlorinated biphenyls (PCBs)	1.04 (0.87, 1.26)	0.95 (0.78, 1.17)	–9%	
Propionaldehyde ^d	1.92 (1.33, 2.77)	2.01 (1.23, 3.28)	1.49 (1.04, 2.14)	4%	0.62	Xylenes	1.49 (1.04, 2.14)	0.87 (0.53, 1.43)	–54%	

Note: All models include the log-transformed air toxic, contrasting the levels of air toxics listed in Table S2 (usually 75% vs. 25%), with a random effect for family, and adjust for the mean air toxic level in the family and the census block group population density, education level, and median rent. An air toxic was evaluated in two-pollutant models and included in this table if its OR from the main model excluded the null and the partial correlation between a pair of air toxics was ≥ 0.4 . ASD, Autism Spectrum Disorder; aOR, adjusted odds ratio; CI, confidence interval; OR, odds ratio.

^aSample size was held constant between models.

^bChange in estimate is calculated as $100 \times \text{natural log of } [(\text{two-pollutant aOR}) / (\text{single-pollutant aOR})]$.

^cThe partial correlation between Pollutant A and Pollutant B, taking into account the modeling structure.

^dAir toxics that were considered significantly associated with autism diagnosis following false discovery rate correction in primary analyses (Table 2).

that did not comprehensively adjust for the entire suite of air toxics. Additional caution is warranted because propionaldehyde and MTBE did not show consistent associations with ASD in the two previous studies that examined them (see Table S1) (Kalkbrenner et al. 2010; Roberts et al. 2013).

Our sample size was not large enough to conduct a comprehensive mixtures analysis given the large number of air toxics (155). (One review of current statistical approaches to environmental mixtures only included 14 exposures in simulated datasets, and yielded inconsistent results) (Taylor et al. 2016). One limitation of our focused two-pollutant approach was residual confounding, caused by measurement error in the adjusted air toxic, and also due to not adjusting for air toxics that did not meet our criteria to include in two-pollutant models or were not included in the NATA model. Additional limitations included the inability to disentangle copollutants with high correlations and the role of statistical chance. Yet our approach had strengths. It is a practical demonstration of the feasibility of simultaneously including correlated exposures in models without undue loss of statistical precision.

We report new findings for ASD diagnosis and three nontraffic-related air toxics that all have industrial uses: bromoform (emitted from industrial sources), glycol ethers (widely used industrial solvents) and 1,4-dioxane (an industrial solvent). The polluting source(s) emitting 1,4-dioxane may be important, because this cluster (correlation group F) contained other air toxics with positive associations with ASD: 1,1,1-trichloroethane and pentachloronitrobenzene. Our findings for bromoform, glycol ethers, and 1,4-dioxane are discrepant from the one prior study that examined them, which found null associations (Roberts et al. 2013), and so firm conclusions are not warranted until confirmed in future studies. We additionally report a positive association between ASD diagnosis and dibenzofurans (which arise from large-scale waste and coal combustion in NATA data), which is consistent with the association observed in the same prior study (Roberts et al. 2013).

Several additional solvents have shown associations with ASD in at least two prior studies, but not in our results: 1,3-butadiene, formaldehyde, methylene chloride, and styrene (see Table S1).

Airborne metals have been found to be associated with ASD previously. Cadmium, chromium, lead, and nickel had positive associations in some prior studies (see Table S1), but not in our results. Airborne mercury exposure has shown more consistent links in prior studies and also had a positive association in our data (but at the more lenient significance threshold) that was not attenuated in the copollutant model with 1,1,1-trichloroethane.

Different findings across studies could arise from several factors, such as differences in geographic coverage, levels of air toxics, time period, study sample characteristics, and statistical design. Our use of the AGRE sample allowed for enhanced confounding control and internal validity by adjusting for family characteristics, including familial susceptibility, but this gain may have been accompanied by a loss in generalizability. Our study population consisted of families with enhanced autism liability given that they had multiple siblings with ASD, and this presumed genetic loading for ASD may have influenced the observed associations. Until empirically demonstrated, we do not currently know whether genetic loading for ASD may overshadow observed risk due to a given environmental exposure, or whether inherited genetic risk enhances observed environmental associations. The few studies of joint effects of air pollutant exposures and genetic variation suggest that both broad susceptibility, based on increased copy number burden, and specific functional variants, may work together with exposure to increase ASD risk (Kim et al. 2017; Volk et al. 2014).

The hierarchical nature of siblings nested within families yielded a unique opportunity to control by design for the family propensity to be exposed to an air toxic, encompassing aspects of socioeconomic status and determinants of neighborhood, possibly to include genetics (Begg and Parides 2003). This likely yielded improved confounding control compared with previous studies of air toxics and ASD that were only able to adjust for measured confounders. We preferred this family propensity design over an alternate design stratified by family. A family-stratified design for this dataset would have excluded families that lacked a case and control, a large proportion in this sample, and would have been overly influenced by discordant exposures within a family, a condition that may introduce bias (Frisell et al. 2012). Examination of environmental exposures in a family-based design, while most often conducted with the overarching goal of detecting gene–environment interactions, increases the statistical power to detect an environmental main effect when a background gene–environment interaction is present (Weinberg et al. 2007). Although the use of a sibling control can protect against shared familial confounding factors, it can also help to protect against bias when the exposure of interest is associated with background population structure. As an example with relevance to this study of air pollution, some literature suggests that genetic inheritance may influence the choice of geographic location (e.g., urban vs. rural home residence), a major determinant of air pollutant exposures (Sariaslan et al. 2016; Whitfield et al. 2005). As has been shown for detection of gene–environment effects, inclusion of a family-based measure of the exposure distribution (as in our analysis) protects against such bias for detection of gene–environment effects (Shi et al. 2011). In our case, inclusion of the average family exposure can be interpreted similarly and may reflect both heritable and nonheritable influences of the air pollution–ASD relationship, including that of the maternal genome on perinatal exposure or population genetic influences that regulate exposure response to air pollution. Such advantages are unique to sibling designs (Weinberg 2012) and unique to this study of air pollution and ASD.

Whether males or females are more susceptible to the impacts of an environmental chemical exposure with regard to autism diagnosis is an important question, prompted in part by the consistent observations that males are four to five times more likely to be diagnosed with autism. We did not find sex modification for the air toxics with the strongest associations with ASD. A more important observation may be that across almost every air toxic, associations were stronger for males: results consistent with those of Roberts et al. (Roberts et al. 2013). Together these findings suggest that males may be more susceptible to airborne pollutants.

In addition to examining ASD diagnosis, we evaluated associations of air toxics with measures of ASD-related traits (using the SRS) and with a measure of autism severity (the CSS). Behavior is difficult to measure, and the multiple continuous measures of phenotypic dimensions are a novel contribution to the assessment of effects of environmental chemicals and neurodevelopment (Sagiv et al. 2015). Because the AGRE sample comprised participants with ASD and their unaffected siblings, the SRS scores followed a bivariate distribution with a mean much higher than a typical population. This constriction in the full range of scores may partly explain why the SRS was a nonsensitive endpoint for assessing the impacts of air toxics in this sample. In contrast, the CSS is a measure of severity used only among cases. The CSS may be capturing a distinct domain of neurodevelopmental impairment, and was only moderately correlated with the SRS score in these data. A role for air toxics in increasing the severity of autism symptoms is important to identify because it may provide pathophysiological insights or avenues for reducing the

burden of autism morbidity. Air toxics emerging as risk factors for greater autism severity (CSS score) were manufacturing chemicals: carbon disulfide and chlorobenzene. Findings for these chemicals were consistent in direction for the other autism endpoints in our data, strengthening the evidence that these air toxics may deserve future study.

We observed inverse (protective) associations between ASD diagnosis and several air toxics: 1,4-dichlorobenzene, 4,4'-methylene diphenyl diisocyanate (MDI), benzidine, and ethyl carbamate (urethane) and for 1,4-dichlorobenzene with autism severity. These associations persisted after controlling for the FDR and after adjusting for correlated air toxics. We cannot rule out that these findings reflect true protective effects, although previous findings from the one prior study that included these do not support this (Roberts et al. 2013) (see Table S1). Alternately, these inverse findings (in addition to the risk associations observed) could be influenced by residual confounding or error in the air toxics model used.

The NATA model has been validated against measured air toxics and shows good agreement for many air toxics. Yet uncertainties remain given that existing validation studies show that accuracy is not equally good for all air toxics and varies geographically (Payne-Sturges et al. 2003; Pratt et al. 2000; Rosenbaum et al. 1999; State of New Jersey 2001). Exposure measurement error arises from NATA model uncertainties, limitations in the emissions inputs, and from using a census-tract average to represent individual exposure. Yet in most areas of the United States for the study period, NATA is the only source of human exposure estimates for many air toxics, and for this reason has been used in at least four prior studies of air toxics and ASD (see Table S1).

Additional exposure measurement error may arise from applying NATA estimates in a given year to births that occurred up to 2 y earlier or later. Our sensitivity analysis showed that associations remained when analyses were restricted to children born in birth years better aligned with NATA estimates, adding to the robustness of these findings. Associations were generally of greater magnitude in this sensitivity analysis, which is consistent with expectations that greater exposure measurement error in the larger sample would result in a small bias toward the null.

Our results likely underestimate the effect of some air pollutants, leading to false negatives. We cannot know for which air toxic the effect estimates were attenuated, and are therefore unable to definitively screen out air toxics that are truly not risk factors for ASD diagnosis or phenotype. False positive associations, however, are not likely due to exposure measurement error, because this would require that the degree of error differed for those diagnosed with ASD versus those without. This differential error is unlikely given that the air toxics assessment and autism measurements were independent.

We focused on producing valid estimates of ASD effects for 155 air toxics, which involved multiple statistical comparisons. We accounted for the potential of falsely identifying a risk factor using a FDR method (Benjamini and Hochberg 1995). Although this method ensures with high probability that most of our findings are not due to statistical chance, it does not guarantee this simultaneously for all findings. The method predicts a 65% probability that at least one finding is false.

In summary, our results corroborate prior findings that traffic emissions may lead to ASD, further implicating propionaldehyde and MTBE as individual air toxics that may be contributing to such effects. We also found that nontraffic-related air toxics may be risk factors for ASD, confirming a previous report of a role for dibenzofurans and newly reporting associations for bromoform, glycol ethers and 1,4-dioxane with ASD diagnosis. We have expanded the scope of work on air toxics and ASD to consider

measures of the autism phenotype in order to explore how risks for disease may differ from those for severity, finding that autism severity may be influenced by carbon disulfide and chlorobenzene. The novel use of a multiplex sample and associated statistical approach to control confounding may account for differences in results from prior studies and may limit generalizability. Although we did not confirm associations with several metals and volatile organic compounds detected in prior studies, our null findings cannot be considered definitive given potential exposure measurement error and differences in the population and analytical design.

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